

## Hydrochlorothiazide Is Superior to Isradipine for Reduction of Left Ventricular Mass: Results of a Multicenter Trial

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**Objectives.** We sought to determine the efficacy of isradipine in reducing left ventricular (LV) mass and wall thickness in hypertensive patients.

**Background.** LV hypertrophy on the echocardiogram is a strong predictor of cardiovascular events. Reduction of LV mass may be a desirable goal of drug therapy for hypertension. However, although thiazide diuretic drugs have been advocated as first-line therapy for hypertension, their efficacy in reducing LV mass has been questioned.

**Methods.** Patients with mild to moderate diastolic hypertension and LV mass in excess of 1 SD of normal values were randomized to isradipine (n = 89) or hydrochlorothiazide therapy (n = 45). Evaluations were obtained at baseline, after 3 and 6 months of treatment and 2 weeks after treatment was stopped.

**Results.** At 6 months, LV mass decreased by  $43 \pm 45$  g (mean  $\pm$  SD) with hydrochlorothiazide ( $p < 0.001$ ) but only by  $11 \pm 48$  g with isradipine ( $p = \text{NS}$ ; between-group comparison,  $p < 0.001$ ). Two weeks after drug therapy was stopped, LV mass remained  $24 \pm 41$  g lower than that at baseline in the hydrochlorothiazide group ( $p = 0.003$ ) but only  $7 \pm 50$  g lower in the isradipine group ( $p = \text{NS}$ ). Septal and posterior wall thicknesses were significantly and equally reduced with both isradipine and hydrochlorothiazide.

Greater LV mass reduction with hydrochlorothiazide was related to a  $2.8 \pm 3.3$ -mm reduction of LV cavity size with hydrochlorothiazide but no reduction with isradipine. At 6 months of treatment, diastolic blood pressure (BP) by design was equally reduced in both treatment groups. At 3 months, systolic BP was reduced by  $17 \pm 15$  mm Hg with isradipine and by  $26 \pm 15$  and  $25 \pm 17$  mm Hg at 3 and 6 months, respectively, with hydrochlorothiazide ( $p = 0.003$ , between-group comparison). However, on stepwise multivariable regression analysis, treatment selection (partial  $r^2 = 0.082$ ,  $p = 0.001$ ), change in average 24-h systolic BP (partial  $r^2 = 0.032$ ,  $p = 0.029$ ) and change in average sitting systolic BP (partial  $r^2 = 0.017$ ,  $p = 0.096$ ) were predictive of LV mass reduction.

**Conclusions.** Despite an equivalent reduction of diastolic BP, 6 months of therapy with hydrochlorothiazide is associated with a substantial reduction of LV mass, greater than that with isradipine. The superior efficacy of hydrochlorothiazide for LV mass reduction is associated with a greater reduction of systolic BP as well as drug selection itself. These data may have important therapeutic implications.

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Increased left ventricular (LV) mass, even below partition values used to define the presence of hypertrophy, is an important predictor of cardiovascular morbidity and mortality (1-3). Moreover, some studies (4,5) suggest that regression of LV hypertrophy and mass may produce benefits over and above those derived from control of hypertension alone.

Although not all antihypertensive drugs are effective for reduction of LV mass (6), previous studies have indicated that

dihydropyridine calcium antagonists (7,8) including isradipine (9), can be effective. Some reports are conflicting (10); however, several (11-14) have indicated that thiazide diuretic drugs are minimally effective in reducing LV mass. Moreover, even with reduction of LV mass, it has been suggested (13) that diuretic drugs may act through volume depletion without decreasing LV wall thickness.

However, many studies of LV mass reduction have been criticized for methodologic limitations, including short duration (often 6 to 12 weeks), inadequate control subjects, small numbers of patients and uncertain blinding (11,15). Moreover, most previous studies have failed to adjust for covariates other than drug selection, such as body weight and systolic blood pressure (BP), which are known to influence LV mass (16,17).

The present study was designed to test the hypothesis that

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#### Abbreviations and Acronyms

BP	=	blood pressure
ECG	=	electrocardiogram
LV	=	left ventricular

in patients in whom isradipine (a dihydropyridine calcium channel blocking agent) produces adequate reduction of diastolic BP, the drug might also be effective for the reduction of LV mass and wall thickness, without adversely affecting LV function. The study was a randomized, double-blind, diastolic titration, parallel-group study of 134 patients with mild to moderate hypertension conducted in 18 centers across the United States. The trial was 6 months in duration and recruited patients with established hypertension and relatively high LV mass. Hence, use of a placebo with absence of BP control for that period was not ethically feasible. However, because hydrochlorothiazide is known to be effective for control of BP but believed to be ineffective for reduction of LV mass, it was selected as an alternative to placebo for comparison with isradipine. To enhance the study's power to detect changes with isradipine, a 2:1 randomization scheme was utilized.

## Methods

**Patient eligibility.** Male and female patients, 21 years or older, with uncomplicated systemic hypertension were eligible for the study. Female patients had to be postmenopausal or surgically sterilized. To qualify for the study, patients had to demonstrate a sitting diastolic BP between 90 and 114 mm Hg (inclusive) at previous clinical evaluations and at the last two visits of the placebo run-in period and a mean awake 24-h ambulatory BP monitoring diastolic reading  $>90$  mm Hg at the baseline visit.

It was assumed that reduction of LV mass would be more readily demonstrated in patients with a relatively high LV mass at baseline. Hence, a partition value for LV mass of  $119 \text{ g/m}^2$  (body surface area) for men and  $98 \text{ g/m}^2$  for women was arbitrarily selected to ensure relatively a high LV mass but not to unduly limit recruitment by restricting patients to those who exceeded the partition value for LV hypertrophy. The partition value for LV mass, normalized for body surface area, was determined as the average plus 1 SD of LV mass previously established by Devereux et al. (18) for normal subjects. The echocardiogram for this determination was acquired at the end of the screening period. If the patient fulfilled all criteria for entry into the study, a second echocardiogram was acquired at the end of the placebo run-in period. This second pretreatment study served as the "baseline" echocardiogram to minimize regression to the mean.

**Study exclusions.** Patients were excluded from the study if one or more of the following criteria were present: malignant or accelerated hypertension; secondary forms of hypertension; severe cardiac disease such as angina pectoris; history of

myocardial infarction; percutaneous transluminal coronary angioplasty; bypass surgery or stroke in the last 6 months; symptomatic congestive heart failure; systolic BP  $>199$  mm Hg or diastolic BP  $>114$  mm Hg; any medical condition that would compromise participation; or an echocardiogram of insufficient technical quality.

**Study design.** After a screening phase, suitable patients underwent a placebo run-in period during which they underwent clinical and laboratory assessment, serial BP measurement and 24-h ambulatory BP monitoring. Patients who met BP criteria for the study on ambulatory BP monitoring underwent screening two-dimensional targeted M-mode echocardiography to determine eligibility.

**Interventions.** Patients were randomized at a ratio of 2:1 to receive isradipine ( $n = 159$ ) or hydrochlorothiazide ( $n = 82$ ). Compliance was monitored by pill count at each visit. The study drug dose was titrated every 2 weeks to obtain BP control, which was defined as a sitting diastolic BP  $<90$  mm Hg and at least 5 mm Hg below the baseline value for patients with a baseline value of 90 to 94 mm Hg; or  $<95$  mm Hg and at least 10 mm Hg below the baseline value for patients with a baseline value of 95 to 114 mm Hg. Isradipine was titrated as needed from 2.5 mg twice a day to 5, 7.5 or 10 mg twice daily and hydrochlorothiazide from 25 mg once a day to 50 mg daily. At the end of the titration phase, patients continued to take the lowest dose of isradipine or hydrochlorothiazide that controlled their BP. If BP was not controlled at the highest allowed dose, the patient was censored from the study.

After completing the titration phase, patients were seen every 4 weeks during a 6-month maintenance phase for measurement of BP and heart rate and assessment of compliance and side effects. At 3 and 6 months of the maintenance period, all patients underwent echocardiography and 24-h ambulatory BP monitoring.

**Posttreatment procedures.** After the 6-month maintenance period, all patients entered a 2-week placebo washout period, at the end of which a brief history and physical examination, clinic BP measurements and laboratory tests were performed, and another echocardiogram was acquired.

**Echocardiography.** Two-dimensional targeted M-mode echocardiography was performed with the patient in the partial left lateral decubitus position. The M-mode cursor was directed through the center of the two-dimensional parasternal short-axis image at or just distal to the tips of the mitral valve leaflets, with strip chart recording on paper at 50 mm/s. Particular care was taken to achieve image planes orthogonal to the LV anatomic long axis and to optimize definition of endocardial and epicardial interfaces.

Using the apical four-chamber view, mitral inflow was sampled by placing the Doppler pulsed wave sample volume in the LV at the level of the mitral annulus (19), with optimal adjustment of gain and filtration to achieve the acoustically purest frequency and narrowest spectral envelope obtainable. Continuous wave Doppler from the apical window was used to record the signals of aortic valve closure and mitral valve opening simultaneously (19).

Echocardiograms were interpreted at the echocardiography central reading laboratory. The average of 3 beats was utilized for all measurements. To minimize variability, studies were measured by a single, experienced sonographer reader. Measurement of ventricular septum, LV cavity, posterior wall and left atrium were performed according to American Society of Echocardiography criteria (20). The peak velocity (E) of early diastolic filling was taken at the maximal excursion of the leading edge of the mitral time-velocity integral, and the late diastolic peak filling rate (A) was determined from the maximal excursion of the time-velocity integral with atrial contraction. The interval was determined between the onset of the QRS complex on the simultaneously recorded electrocardiogram (ECG) and the onset of Doppler mitral flow, as well as the interval between the QRS onset and Doppler aortic closure. The isovolumetric relaxation time was determined as the difference between these intervals. After comparability with the real-time two-dimensional echocardiographic parasternal images on videotape was determined, M-mode paper strip chart recordings were analyzed utilizing a commercially available off-line analysis system (Microsonics Datavue II) coupled to a digitizing tablet with a spatial resolution of 0.001 in. (0.0025 cm).

Using the formula of Devereux et al. (21), LV mass (g) was calculated as  $0.80 \times (1.04 \times [(\text{Septal thickness} + \text{LV cavity diameter} + \text{Posterior wall thickness})^3 - (\text{LV cavity diameter})^3] + 0.6 \text{ g})$  and normalized by body surface area determined by nomogram (22). Meridional end-systolic wall stress, LV fractional shortening, cardiac output and peripheral resistance were computed as previously described (23).

Intraobserver errors for septal and posterior wall thicknesses and LV diastolic dimension were 8.2%, 6.9% and 2.3%, respectively. Interobserver errors (comparison with reader J.S.G.) were 9.1%, 8.7% and 7.9% respectively. For E and A peak diastolic velocities, the intraobserver errors were 8.7% and 7.9%, respectively. The Pearson coefficient for intraobserver correlation of LV mass was 0.82, diastolic dimension 0.80, posterior wall 0.84, septal wall 0.83, E velocity 0.76 and A velocity 0.86.

**Ambulatory BP monitoring.** Ambulatory BP monitoring was performed using commercially available equipment (SpaceLabs, Advanced Technology Laboratories), and analyses was carried out by a central laboratory. BP was recorded at 30-min intervals and analyzed as the average of 24-h recording, the average of awake BP (8 AM to 10 PM) and average early morning hour BP (4 AM to 10 AM).

**Clinical measurements.** BP, body weight, electrolytes and an ECG were obtained at every visit. BP was recorded with a mercury sphygmomanometer in both sitting and standing positions, according to American Heart Association guidelines with systolic BP defined as phase I and diastolic BP as phase V Korotkoff sounds.

**Statistical analysis.** Results are presented as mean value  $\pm$  SD. Comparative data were analyzed by two-way repeated measures analysis of variance. Between-group comparisons

**Table 1.** Demographic Characteristics: Evaluable Patients\*

	Isradipine (n = 89)	Hydrochlorothiazide (n = 45)
Male	74 (83%)	34 (76%)
Female	15 (17%)	11 (24%)
White	28 (32%)	9 (20%)
Black	61 (68%)	35 (78%)
Other		1 (2%)
Age (yr)	56 $\pm$ 11	58 $\pm$ 9
Duration of HTN (yr)	11 $\pm$ 9	13 $\pm$ 8
Height (cm)	170 $\pm$ 7.5	172.5 $\pm$ 10
Weight (kg)	89.7 $\pm$ 16	91 $\pm$ 13.6
Sitting SBP (mm Hg)	158 $\pm$ 16	161 $\pm$ 17
Sitting DBP (mm Hg)	101 $\pm$ 7	101 $\pm$ 6
Sitting HR (beats/min)	74 $\pm$ 9	78 $\pm$ 9

\*p = NS for all comparisons. Data presented are mean value  $\pm$  SD or number (%) of patients. DBP = diastolic blood pressure; HR = heart rate; HTN = hypertension; SBP = systolic blood pressure.

were made using Bonferroni correction for multiple comparisons.

The independent contribution of change of descriptors to change in LV mass and its components was assessed using stepwise multivariate regression analysis. The variables entered into the model were change in casual systolic and diastolic BP, change in 24-h average systolic and diastolic BP, change in body weight, treatment selection, race, gender and age.

Analysis of variance, covarying for treatment effect as well as race, age and gender, was performed for change in BP variables against change in LV mass. If selection of therapy had no effect on LV mass independently of the magnitude of change in BP, the treatment effect would be expected to be nonsignificant.

All statistical tests were two-sided. Differences resulting in p values  $\leq 0.05$  were considered significant, except for tests involving interactions, which were done at a significance level of 0.10. All variables were evaluated using the actual measurements and the change from baseline.

The statistical computer package SAS, versions 5 and 6, was used to generate the statistical analyses (24).

## Results

Two hundred forty-one patients from 18 centers entered the study. Of these, 159 were randomized to isradipine and 82 patients to hydrochlorothiazide. A total of 43 patients taking isradipine (27%) and 28 hydrochlorothiazide (34.1%) withdrew from the study primarily for uncontrolled hypertension, patient request or side effects. There were 36 patients (27 taking isradipine, 9 hydrochlorothiazide) who completed the study but had inadequate echocardiographic data; they were thus excluded from the efficacy analysis.

A total of 134 patients (89 receiving isradipine, 45 receiving hydrochlorothiazide) had complete echocardiographic and clinical data and were considered evaluable. The average dose of isradipine used after drug titration was  $6.8 \pm 2.5$  mg twice

**Table 2.** Baseline Echocardiographic Variables\*

	Isradipine (n = 89) (mean ± SD)	Hydrochlorothiazide (n = 45) (mean ± SD)
Septum (mm)	13.3 ± 2.0	12.9 ± 2.0
Posterior wall (mm)	12.6 ± 1.9	12.3 ± 1.7
Left atrium (mm)	43.0 ± 6.1	42.1 ± 5.4
Aortic dimension (mm)	33.9 ± 5.0	33.9 ± 3.9
LV diastolic dimension (mm)	51.3 ± 5.8	52.2 ± 5.6
LV systolic dimension (mm)	32.1 ± 6.1	33.0 ± 6.2
LV mass (g)	345 ± 80	343 ± 89
LV mass index (g/m <sup>2</sup> )	170 ± 36	165 ± 36

\*p = NS for all comparisons. LV = left ventricular.

daily and that of hydrochlorothiazide was  $41 \pm 12$  mg daily. Tables 1 and 2 present the demographic characteristics and echocardiographic variables of the evaluable patients at baseline. There were no differences between the two treatment groups.

**Effects on BP.** Table 3 presents BP changes from baseline at 3 and 6 months of maintenance therapy and at the end of the 2-week placebo washout phase after the completion of active therapy. Both isradipine and hydrochlorothiazide reduced sitting systolic BP significantly, but the reduction with hydrochlorothiazide was greater at all study intervals. Diastolic BP was reduced significantly with both treatments and to the same extent.

On 24-h ambulatory BP monitoring there was significant reduction of average systolic and diastolic BP at 3 and 6 months of maintenance therapy in both treatment groups. However, there was a greater reduction in systolic BP with hydrochlorothiazide at 6 months (Table 3) during awake and early morning hours.

**Effects on LV mass and left atrial size.** At 3 months, LV mass was reduced significantly with both treatments (Fig. 1,

Table 4), but at 6 months, there was reduction of LV mass only with hydrochlorothiazide. At 2 weeks after treatment, the change in LV mass with isradipine was not statistically different from LV mass at baseline, whereas with hydrochlorothiazide LV mass remained less than that at baseline.

Although an equivalent decrease in wall thickness occurred with both drugs at 6 months, LV diastolic dimension was reduced significantly only with hydrochlorothiazide treatment and returned to baseline at 2 weeks after therapy.

Decrease in left atrial dimension occurred at 3 and 6 months with hydrochlorothiazide but not with isradipine (Table 4).

**LV function.** With isradipine there was a small increase in fractional shortening at 3 months ( $-0.017 \pm 0.07$ ,  $p = 0.048$ ), accompanied by decreases in end-systolic stress ( $-7.9 \pm 18.1 \times 10^3$  dynes/cm<sup>2</sup> at 3 months;  $-5.0 \pm 21 \times 10^3$  dynes/cm<sup>2</sup> at 6 months, both  $p \leq 0.04$ ). Although end-systolic wall stress also decreased with hydrochlorothiazide ( $-11.8 \pm 21.0 \times 10^3$  dynes/cm<sup>2</sup> at 3 months,  $-12.3 \pm 19.0 \times 10^3$  dynes/cm<sup>2</sup> at 6 months, both  $p \leq 0.001$ ), there were no significant increases in fractional shortening, possibly consequent to decreases in LV volume.

**Diastolic LV filling.** Decreases in peak late diastolic filling with isradipine and hydrochlorothiazide were not statistically significant. Patients receiving hydrochlorothiazide evidenced decreases in early diastolic peak filling velocity of  $5.1 \pm 11$  cm/s ( $p = 0.009$ ) at 3 months and  $5.8 \pm 13$  cm/s at 6 months ( $p = 0.015$ ). Isovolumetric relaxation time at baseline ( $94 \pm 24$  ms) did not differ between treatment groups. There were no significant changes during or after treatment with either drug and no significant between group differences.

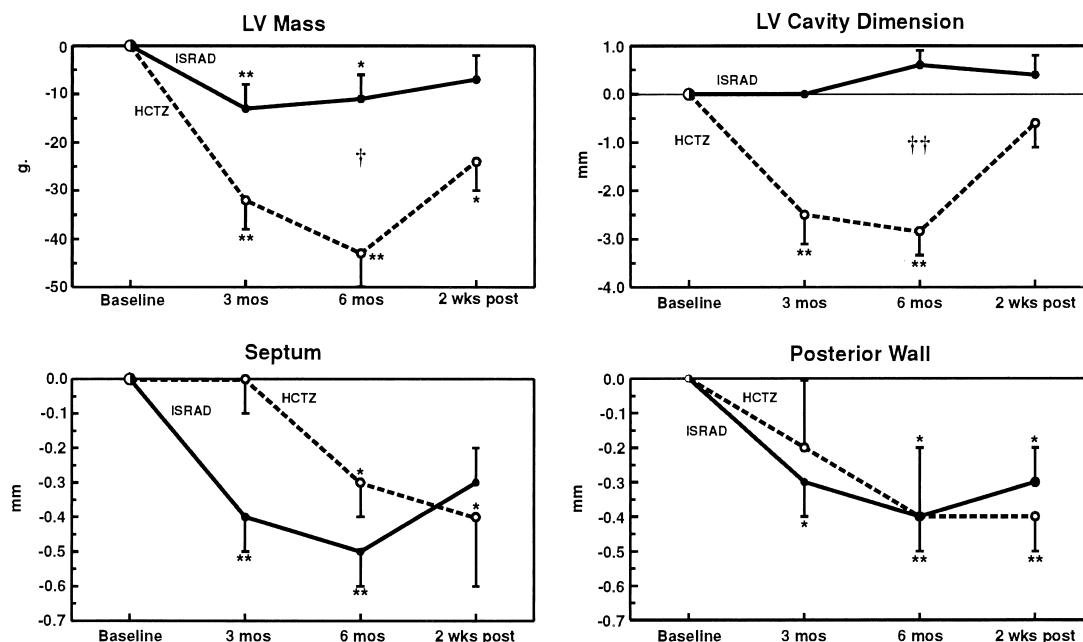
**Descriptors of change in LV mass.** Treatment selection significantly affected the slope relation of BP variables to change in LV mass at 6 months (analysis of covariance). On stepwise multivariable regression analysis, treatment selection

**Table 3.** Change From Baseline in Blood Pressure Measurements

	Isradipine (mean ± SD)	p Value (Δ from baseline)	Hydrochlorothiazide (mean ± SD)	p Value	
				Δ From Baseline	Between-Group Δ*
Sitting SBP (mm Hg)					
3 mo	-17.4 ± 15	<0.001	-26.0 ± 14.8	<0.001	0.003
6 mo	-17.6 ± 16	<0.001	-25.3 ± 16.9	<0.001	0.006
2 wk post	-1.6 ± 16	0.291	-7.7 ± 14.5	<0.001	0.055
Sitting DBP (mm Hg)					
3 mo	-12.9 ± 8.1	<0.001	-13.2 ± 6.4	0.001	0.51
6 mo	-12.4 ± 8.7	<0.001	-13.1 ± 6.9	0.001	0.53
2 wk post	-3.8 ± 9.6	<0.001	-5.0 ± 7.2	0.001	0.62
Ambulatory BP monitoring					
Average SBP, 4 AM-10 AM (mm Hg)					
3 mo	-16 ± 13	<0.001	-23 ± 14	0.001	<0.001
6 mo	-14 ± 15	<0.001	-23 ± 11	0.001	<0.001
Average SBP, 8 AM-10 PM (mm Hg)					
3 mo	-15 ± 12	<0.001	-22 ± 11	0.001	<0.001
6 mo	-15 ± 13	<0.001	-23 ± 11	0.001	<0.001

\*There were no differences between the two groups in diastolic blood pressure during ambulatory monitoring. BP = blood pressure; post = after completion of active therapy; Δ = change; other abbreviations as in Table 1.





**Figure 1.** Change in LV mass and its components (septal wall thickness, posterior wall thickness, LV cavity dimension) during and after treatment. HCTZ = hydrochlorothiazide; ISRAD = isradipine. \* $p \leq 0.05$ , \*\* $p \leq 0.001$  versus baseline. † $p \leq 0.001$  between treatment groups.

(partial  $r^2 = 0.082$ ,  $p = 0.001$ ), change in average 24-h systolic BP (partial  $r^2 = 0.032$ ,  $p = 0.029$ ) and change in average casual systolic BP (partial  $r^2 = 0.017$ ,  $p = 0.096$ ) were predictors of change in LV mass. Gender, race, age and change in body weight did not enter the model at the 0.10 level of significance. Separate analysis of the components of LV mass showed a significant treatment effect of hydrochlorothiazide on LV diastolic dimension.

## Discussion

Despite previous expectations and a study design intended to maximize the ability to detect the effects of isradipine versus the “control” arm (hydrochlorothiazide), the results of the present study showed that reduction of LV mass was in fact fourfold greater with hydrochlorothiazide than with isradipine. Moreover, reduction of LV mass at 3 months with isradipine did not persist at 6 months of therapy. Importantly, the small decrease in LV mass with isradipine was due to a decrease in septal and posterior wall thickness, with no change in LV cavity size, whereas with hydrochlorothiazide the decrease in LV mass was due to a decrease in both wall thickness and LV cavity dimension. This finding underscores the importance of the preload contribution to LV mass and hypertrophy previously emphasized by Ganau et al. (25).

Analysis of treatment differences in LV mass after adjusting for weight, BP, race and gender showed that the magnitude of decrease in systolic BP reduction was a significant predictor of

LV mass reduction with hydrochlorothiazide. However, even after adjustment for systolic BP, drug selection itself remained independently predictive of LV mass reduction, suggesting that factors other than reduction of systolic BP, or the other covariates that were analyzed, may be associated with the efficacy of hydrochlorothiazide for LV mass reduction. Nonetheless, better reduction of systolic BP with hydrochlorothiazide is also of importance given the contribution of systolic BP to the morbidity of hypertension.

**Previous studies.** In many studies (13,14), diuretic drugs have been relatively ineffective for reduction of LV mass. Moreover, there is a theoretic basis (26,27) for ineffective regression of LV hypertrophy with diuretic drugs, whereby diuretic drugs either fail to inhibit neurohormonal mechanisms of hypertrophy or actually result in their reflex activation (27).

However, our finding of a substantial reduction in LV mass with a diuretic drug is in agreement with that of the Treatment of Mild Hypertension Study (TOMHS) of 844 patients. Although patients in all treatment arms showed reduction of LV mass (28), LV mass decreased more than placebo only in the chlorthalidone treatment group (29).

The Department of Veterans Affairs trial of monotherapy in mild to moderate hypertension (31), a trial of six active drugs (30), also found that the diuretic drug (hydrochlorothiazide) was effective for reduction of LV mass, whereas the calcium blocker (diltiazem) was not.

**Effects on LV function.** In theory, loss of contractile protein with LV mass reduction may place the left ventricle at risk for sudden increases in afterload. However, in the present study, as in others (8,15,32), LV systolic chamber function (fractional shortening) was not diminished in either treatment group, even after discontinuation of therapy. During treatment, the small increase in fractional shortening with isradipine that accompanied the decrease in end-systolic stress may

**Table 4.** Change From Baseline in Echocardiographic Measurements

	Isradipine (n = 89)		Hydrochlorothiazide (n = 45)		
	Mean ± SD	p Value (Δ from baseline)	Mean ± SD	p Value	
				Δ From Baseline	Between-Group Δ
Septum (mm)					
3 mo	-0.4 ± 1.0	0.003	-0.0 ± 0.7	0.866	0.117
6 mo	-0.5 ± 1.1	<0.001	-0.3 ± 0.8	0.05	0.409
2 wk post	-0.3 ± 1.4	0.226	-0.4 ± 1.0	0.007	0.515
Posterior wall, diastole (mm)					
3 mo	-0.3 ± 1.1	0.069	-0.2 ± 1.1	0.166	0.839
6 mo	-0.4 ± 1.3	0.006	-0.4 ± 1.1	0.039	0.982
2 wk post	-0.3 ± 1.3	0.06	-0.4 ± 0.9	0.009	0.964
Left atrium (mm)					
3 mo	0.0 ± 3.9	0.987	-1.8 ± 3.8	0.009	0.039
6 mo	0.9 ± 4.4	0.061	-1.8 ± 3.5	0.006	0.003
2 wk post	0.4 ± 4.4	0.71	-0.8 ± 3.4	0.405	0.516
LV diastolic dimension (mm)					
3 mo	0.0 ± 3.6	0.993	-2.5 ± 3.6	<0.001	<0.001
6 mo	0.6 ± 3.3	0.116	-2.8 ± 3.3	<0.001	<0.001
2 wk post	0.4 ± 3.6	0.48	-0.6 ± 3.1	0.609	0.391
LV mass (g)					
3 mo	-12.9 ± 47.3	0.036	-31.6 ± 41.8	<0.001	0.078
6 mo	-10.6 ± 48.2	0.123	-43.4 ± 44.7	<0.001	<0.001
2 wk post	-7.1 ± 50.2	0.362	-24.0 ± 41.0	0.003	0.286
LV mass index (g/m <sup>2</sup> )					
3 mo	-6.8 ± 24.0	0.033	-14.3 ± 20.2	<0.001	0.075
6 mo	-5.8 ± 24.7	0.12	-19.8 ± 21.2	<0.001	<0.001
2 wk post	-4.3 ± 25.5	0.224	-11.4 ± 19.2	0.003	0.35

Abbreviations as in Tables 2 and 3.

reflect decreased afterload consequent to vasodilation. Although the failure of fractional shortening to increase with hydrochlorothiazide despite a decrease in end-systolic stress could be interpreted as depression of myocardial function, it also could be due to decreased preload consequent to the decrease in LV volume.

LV diastolic filling velocity measured by Doppler reflects complex interactions of loading, heart rate, autonomic tone, myocardial distensibility, active relaxation and other factors (33). Hence, it is difficult to offer a meaningful physiologic explanation for the observed effects of isradipine and hydrochlorothiazide on LV filling. However, the greater decrease in early diastolic peak filling velocity with hydrochlorothiazide than with isradipine may have been consequent to volume effects of hydrochlorothiazide.

**Limitations of the study.** Because the study design specified a cutoff value for LV mass as an inclusion criterion, there is the risk that changes in LV mass, particularly the relatively small decrease with isradipine at 3 months, could be due to a regression to the mean. However, this is considered unlikely because two pretreatment echocardiograms were obtained—one to determine the selection criterion for LV mass and the second to use as a baseline value. Also, some but not all echocardiographic measurements used to calculate LV mass decreased with isradipine. Moreover, regression to the mean

could not account for the large difference in LV mass reduction between treatment groups.

Additionally, the study dropouts due primarily to inadequate BP control (44% with isradipine, 45% with hydrochlorothiazide) may limit the generalizability of the study. However, the success of the initially assigned drug in achieving and maintaining diastolic BP is consistent with that found previously (30). Furthermore, the study design permitted evaluation of the drug actually used, without confounding of study results by crossovers to medication not initially assigned or by use of additional medication.

**Clinical implications.** Because LV mass incrementally adds to the cardiovascular risk of hypertension, and reduction of LV mass may confer benefits above and beyond those attributed to BP control alone, it seems reasonable to use drugs that are particularly effective for reduction of LV mass as well as reduction of BP.

Data from the present study and others suggest that diuretic drugs are more effective than some other drugs in reducing LV mass. This, together with the dramatic reductions in stroke and cardiac events (34,35) associated with diuretic drug use, particularly in elderly hypertensive patients with a high prevalence of LV hypertrophy, as well as the lower cost of diuretic drugs, strengthens recommendations (36) for the use of diuretic drugs as first-line therapy in hypertension.

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## Appendix

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